Impairment of random motor generation in de novo and treated Parkinson's disease

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published in
Neurology
2001

DOI (link to publisher)
10.1212/wnl.57.11.2111

document version
Publisher's PDF, also known as Version of record

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Neurology 2001;57;2111

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Motor perseveration is an early sign of Parkinson's disease

Article abstract—Perseveration in the generation of random motor behavior was examined by means of the Vienna perseverance task in groups of de novo (n = 18) and treated (n = 18) patients with early PD, and in control subjects (n = 18). In comparison with control subjects, both the de novo and treated patients with PD were relatively unable to generate random motor sequences, indicating a decreased ability to switch cortical behavioral programs in PD. An impairment of random motor generation appears to be a very early feature of PD.

NEUROLOGY 2001;57:2111–2113

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The cognitive deficit in nondemented patients with PD can be described as an inability to switch cortical behavioral programs in situations requiring the internal regulation of behavior, which leads to the perseveration of the current behavioral program. Because this type of cognitive disturbance can be found in the early phases of PD,[1] it is tempting to speculate that such cognitive disturbances may even precede the first motor deficits. In an animal model of PD, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkey, cognitive disturbances are indeed present before any clear motor disturbances appear.[2] Considering the 65% loss of nigral dopaminergic neurons at the time of clinical diagnosis, as determined by means of dopamine transport SPECT,[3] a preclinical diagnosis would extend the time window available for the neuroprotective strategies that are under development.[4]

In previous studies, several tasks have been used to measure the capacity for internal guidance of behavior. Patients with PD manifest perseverative behavior on a variety of neuropsychological assessments traditionally believed to reflect frontal lobe function.[5] Most of these tasks, however, provide subjects with implicit rules and logical stimulus–response relations, whereas ideally, a task used to detect disturbances in the internal regulation of behavior would have a minimum of external cues, thereby maximizing the amount of internal (spontaneous) regulation of behavior needed to perform the task. Tasks requiring subjects to generate random behavior may be better suited to this purpose.

Most research into random behavior in PD has focused on random verbal generation of either letters[6] or numbers.[7] Because of the common use of letters and numbers in everyday life, these tasks are prone to confounding effects of prior experience with verbal or numerical tasks. A major pragmatic problem of random letter or number generation is the need to record and key the subject's response, a relatively laborious and potentially error-prone activity.

The Vienna perseverance task is a computerized version of the pointing task developed by Mittenecker and can be used to assess the ability to generate random motor behavior. Using a manual version of this task, disturbances in the generation of random motor actions have previously been found in treated patients with early PD.[8]

In the current study, the Vienna perseverance task was used to determine whether motor perseveration also is present in untreated patients with early PD. In addition, the effect of dopaminomimetic treatment on task performance was studied by comparing the de novo patients with a group of treated patients with early PD.

Methods. *Subject selection.* Groups of nondemented patients with untreated (n = 18) and treated (n = 18) idiopathic PD were selected from the outpatient clinic for movement disorders at the Vrije Universiteit Medical Center. All patients with PD were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria. Eighteen self-declared neurologically healthy subjects served as control subjects. All subjects but one of the

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Supported by the Van Alkemade Foundation.

Received May 28, 2001. Accepted in final form August 17, 2001.

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Table 1 *Subject characteristics*

Characteristics	Control subjects, n = 18	Patients with de novo PD, n = 18	Patients with treated PD, n = 18
Sex, M/F	14/4	14/4	14/4
Age, y, mean ± SD	56 ± 6.2	58 ± 9.4	60 ± 8.3
Education, SOI, mean ± SD	5.9 ± 1.3	6.0 ± 1.1	6.0 ± 1.3
UPDRS motor score, mean ± SD	0.4 ± 0.8	9.8 ± 2.8	12.6 ± 8.8
Disease duration, y, mean ± SD	NA	1.8 ± 1.1	3.9 ± 1.8*
Hoehn and Yahr stage, I/II	NA	16/2	13/5

* Different from patients with de novo PD (two-tailed, $p < 0.000$).

SOI = Standaard Onderwijs Indeling; NA = not applicable.

de novo patients with PD were right-handed. All subjects were matched for sex, age, and education.

Subject characteristics are listed in table 1. Education was measured using the Dutch SOI scale, a standard educational scale. Unified Parkinson's Disease Rating Scale motor scores were obtained by a trained neurologist. Disease duration was calculated on the basis of the patients' subjective estimate of the time of occurrence of the first parkinsonian symptoms. Treated patients were tested during their normal regime of antiparkinsonian medication (i.e., a dopamine agonist, L-dopa, or a combination of the two). In case of motor response fluctuations, patients were tested during their on period. None of the patients or control subjects were using benzodiazepines, antipsychotics, or stimulants.

Vienna perseveration task. The Vienna perseveration task is part of the Vienna test system (Dr. G. Shuhfried Ges.m.b.H, Mödling, Switzerland). Seated in front of a 17-inch monitor, subjects were instructed to randomly press nine circles displayed on screen with a light pen, avoiding the use of systematic or repetitive strategies. The task consisted of 210 consecutive presses that had to be performed at the constant rhythm of a short "bleep" that was offered 64 times per minute. Task duration was approximately 4 minutes, depending on the number of omissions. Each subject was given a practice run (duration approximately 30 seconds) to get accustomed to the instrumentation and the actual test procedure.

Data analysis. Perseverative behavior was assessed by determining the relative redundancies of the first and second order. Relative redundancy of the first order (R1) is a measure of the preference for individual circles. R1 can be calculated by relating the observed degree of randomness [H (X)] to the maximum degree of randomness [H_{max} (X)]:

$$R1\ (X) = \frac{H_{max}\ (X) - H\ (X)}{H_{max}\ (X)}$$

It reaches a minimum when the tapped circles are evenly distributed.

Redundancy of the second order expresses the probability with which circle Y will be selected after a tap on circle X. By dividing the observed value of this variable by its maximum value, the relative redundancy of the second order (R2) is obtained:

$$R2\ (X, Y) = \frac{H\ (X{:}Y)}{H_{max}\ (X{:}Y)}$$

The lower the preference for certain combinations of circles, the more improbable the prediction of variable Y by variable X, and thus the smaller the R2. At an equal distribution of the 81 possible combinations of circles, R2 = 0.

Statistical analysis comprised two-tailed univariate analysis of variance of log 10 transformed data at a significance level of 0.05 and post-hoc analysis of individual group differences by means of Bonferroni (equal variances) or Tamhane's T2 (unequal variances). An estimate of effect size (ES) was based on the linearly independent pairwise comparison among the estimated marginal means.

Results. Means and SDs of motor perseveration scores are listed in table 2. No significant differences were found with respect to the relative redundancy of the first order, indicating no differences in relative preference for certain circles between the three groups. A group difference was found with respect to the relative redundancy of the second order ($F[2,51] = 8.13$; $p \leq 0.001$; ES = 0.49). Post-hoc analysis of group differences revealed a deficit to generate random sequences as expressed by the index of relative redundancy of the second order in the de novo group relative to the control group ($p = 0.001$). Similarly, the average relative redundancy of the second order in the group of treated patients with PD was higher than that of the control group ($p = 0.012$). No significant differences in relative redundancy of the second order between the de novo and treated patients were found. The number of omissions was equal across all groups. Based on these data, an estimate of the diagnostic value of the Vienna perseverance task, using the criterion of maximization of the sum of sensitivity and specificity, yielded a sensitivity of 67% at a specificity of 99% for correctly classifying the patients with de novo PD.

Table 2 *Relative redundancies of the first and second order, means ± SD*

Redundancies	Control subjects, n = 18	Patients with de novo PD, n = 18	Patients with treated PD, n = 18
R1 (%)	0.79 ± 0.43	1.14 ± 1.06	0.93 ± 1.22
R2 (%)	18.92 ± 1.79	29.99 ± 12.91*	26.38 ± 8.12†

* Different from control subjects (two-tailed, $p = 0.001$).
† Different from control subjects (two-tailed, $p = 0.012$).

Discussion. We found an impairment in generating random motor sequences in early-stage treated as well as in untreated patients with PD, confirming previous observations.[6-8] Our study of random motor behavior in PD is of note because we found perseverative tendencies even in patients with early, untreated PD.

The average performance of the treated patients was not better than that of the untreated patients. Although the effect of dopaminomimetics on random motor generation ideally should be determined using a longitudinal approach, we believe a tentative conclusion can be drawn from the current data. Taking into consideration the somewhat longer disease duration in the treated patients, dopaminomimetics would appear to have little, if any, effect on random motor generation.

The generation of random behavior is thought to involve holding information on line, suppression of habitual responses, generation of internally driven responses, monitoring of responses, and modification or switching of production strategies,[9] all of which are attention demanding and likely to involve the so-called supervisory attentional system (SAS). In particular, deficits concerning modification or switching of production strategies and internally driven response generation are thought to be responsible for perseverative tendencies and other cognitive deficits in PD and may therefore reflect dysfunction of the SAS.[10] Because of the complete absence of external stimuli to guide selection of the next response and the need for novelty, in the sense that responses are required to lack any systematic or repetitive strategies, random motor generation appears to be an ideal task for studying dysfunction of the SAS in PD.

Our data, obtained in selected groups of patients with de novo PD and control subjects, suggest that an impairment of random motor generation may be potentially useful as an early diagnostic marker. The ease of administration and the objectivity in scoring and interpretation of the Vienna perseverance task, as well as its short duration, further add to the potential usefulness of this task as (part of) a screening test for PD. Future prospective studies in patients with PD, as well as comparative studies including patients with atypical parkinsonian syndromes, are necessary to determine more clearly the early diagnostic value of the Vienna perseverance task in PD.

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